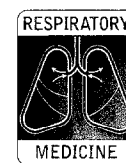


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Effect of single doses of inhaled lignocaine on FEV₁ and bronchial reactivity in asthma

T. W. HARRISON AND A. E. TATTERSFIELD

Division of Respiratory Medicine, Nottingham City Hospital, U.K.

Inhaled lignocaine appeared to have considerable steroid sparing properties in an uncontrolled trial in 20 patients with oral-steroid-dependent asthma. Since it can also cause bronchoconstriction, safety needs to be studied under controlled conditions. We have performed a randomized, double-blind, placebo-controlled study in 20 patients with mild to moderate asthma to determine the effects of single doses of inhaled lignocaine 40 and 160 mg compared to saline. Saline and lignocaine 40 and 160 mg caused an initial fall in FEV₁, mean maximum change being 0.13, 0.19 and 0.23 l respectively with no significant difference between treatments ($P=0.2$). There was no fall in FEV₁ following salbutamol pretreatment and lignocaine had no significant effect on heart rate or blood pressure or on bronchial reactivity to methacholine carried out at 90 min after inhalation. These results show that single doses of inhaled lignocaine are well tolerated in subjects with mild to moderate asthma and that any tendency to bronchoconstriction can be prevented with salbutamol pretreatment.

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Introduction

Severe asthma is difficult to treat and many patients require long-term treatment with oral corticosteroids, sometimes in high doses. Corticosteroids have serious adverse effects but alternative therapies such as azathioprine, methotrexate and cyclosporin have limited ability to reduce maintenance oral corticosteroids and have significant adverse effects of their own (1). In an uncontrolled 2-year study in 20 patients, inhaled lignocaine (between 40 and 160 mg four times a day) allowed 13 of the subjects to stop oral corticosteroids completely (2). In this study only one subject reported chest tightness after lignocaine inhalation.

These findings need to be confirmed in a controlled study, but before doing this more information is needed about the safety of nebulised lignocaine in subjects with asthma. In contrast to the study by Hunt *et al.*, four single-dose studies have demonstrated bronchoconstriction following lignocaine inhalation (3–6). We have performed a double-blind, placebo-controlled study to determine the time-course of the effect of inhaled lignocaine on forced expiratory volume in 1 s (FEV₁), blood pressure and heart rate and its effect on bronchial reactivity to methacholine in 20 subjects with mild to moderate asthma. We also looked at the effect of pretreatment with salbutamol to see whether this would prevent any bronchoconstriction. Lignocaine plasma levels were measured at 30 and 60 min post-inhalation.

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Correspondence should be addressed to: Dr T. W. Harrison, Division of Respiratory Medicine, Nottingham City Hospital, Nottingham NG5 1PB, U.K. Fax: +44 115-960 2140.

Methods

SUBJECTS

Twenty subjects aged 24–62 years with stable asthma and no other relevant illness were studied. Inclusion criteria were: subjects had to be current non-smokers, have an FEV₁ greater than 50% predicted, an increase in FEV₁ of at least 15% in response to 200 µg inhaled salbutamol and a provocative dose of methacholine causing a fall in FEV₁ of 20% (PD₂₀) of 12 µmol or less. Apart from taking short-acting beta-agonists as required, 13 subjects were taking up to 800 µg per day of an inhaled corticosteroid and two were taking a long-acting beta-agonist. Subjects gave written consent to the study which was approved by the Nottingham City Hospital ethics committee.

MEASUREMENTS

FEV₁ was measured with a dry bellows spirometer (Vitalograph, Buckingham, U.K.) as the higher of two readings within 100 ml. The PD₂₀ methacholine was measured by a modification of the method of Yan *et al.* (7). Subjects inhaled three puffs of saline from a DeVilbiss nebuliser (DeVilbiss Health Care Inc, Pennsylvania, U.S.A.) whilst breathing in slowly from functional residual capacity to total lung capacity, followed by doubling doses of methacholine from 0.048 to 12 µmol. FEV₁ was measured 1 min after each dose and the test stopped when it had fallen by 20% from the post-saline value. PD₂₀ was calculated by linear interpolation of the last two readings on the log dose-response plot. Blood pressure and heart rate were recorded by an automated sphygmomanometer

(Lifestat 200, Physio-Contro Corporation, Washington, U.S.A.) and plasma lignocaine levels assayed by fluorescence polarization immunoassay, using the TDx/TDxFLx lignocaine assay (Abbott Laboratories, U.S.A.).

PROTOCOL

The study had a randomized, placebo-controlled, double-blind design. Subjects taking an inhaled steroid kept the dose constant throughout the study whilst short-acting beta-agonists and long-acting beta-agonists were withheld for at least 6 and 14 h respectively before each visit. Subjects attended the laboratory for two screening visits to ensure they fulfilled the inclusion criteria and had a normal physical examination and electrocardiogram. Subjects fulfilling the entry criteria then attended at the same time on 5 study days.

On each study day a cannula (Butterfly®, Abbot Ireland, Sligo, Republic of Ireland) was inserted into a forearm vein followed by a 15-min rest before baseline measurements of FEV₁, heart rate and blood pressure were performed. Subjects then inhaled saline or salbutamol 2.5 mg followed 15 min later by saline or lignocaine hydrochloride 40 or 160 mg (Xylocaine 4% Topical Solution, Astra Pharmaceuticals Ltd, Kings Langley, U.K.) diluted to 4 ml with normal saline. The treatment option of salbutamol followed by saline was not included to reduce the number of visits. All treatments were inhaled via a Pari LC nebuliser with filter and valve set and driven by a Pari Master compressor unit (mass median diameter 3.1 µm, total output 0.5 g min⁻¹; Pari, Starnberg, Germany). In an attempt to disguise the taste and oral anaesthesia associated with inhaled lignocaine, one spray of 4% lignocaine was applied to the subject's tongue whilst they exhaled, immediately before the second nebulisation. FEV₁, blood pressure and heart rate were recorded before and at 5, 10, 15, 30, 45, 60, and 90 min after the second nebulisation and methacholine PD₂₀ was determined at 90 min providing FEV₁ was within 10% of baseline. A venous blood sample was withdrawn at 30 and 60 min, separated and stored at -20°C for subsequent assay of plasma lignocaine concentration. The assays were confined to samples following the 160 mg dose of lignocaine, identified after the study code had been broken. Subjects took nothing by mouth for 1 h post-inhalation.

Twenty subjects were studied to provide at least 95% power to detect one standard deviation (SD) difference in FEV₁ between lignocaine and saline at a significance level of 0.05.

ANALYSIS

The effect of the initial inhalation of salbutamol or saline on FEV₁ is expressed as mean change from baseline with 95% confidence intervals (CI). The effects of the second inhalation of lignocaine or saline on FEV₁, blood pressure and heart rate are expressed as the mean change from the measurements taken immediately prior to the second nebulisation. PD₂₀ values for methacholine were log-transformed for analysis and differences in PD₂₀ measured in doubling doses. Area under the curve was determined for

heart rate and blood pressure and expressed as an average over the 90 min. Treatment effect was determined by two-way ANOVA with a *P*-value of 0.05 considered as statistically significant. Mean values are given with 95% CI.

Results

Twenty subjects (eight female) were entered, although one withdrew after the first day for personal reasons and is excluded from the analysis. Demographical details of the subjects are presented in Table 1. The mean screening FEV₁ was 2.6 l (77% predicted) and baseline FEV₁ values did not differ significantly on the 5 study days.

All patients reported a bitter taste and oropharyngeal numbness following the lignocaine spray to the tongue and nebulised lignocaine and this persisted for approximately 30 min. Subjects were unable to differentiate between inhaled saline and lignocaine 40 mg, whereas most found that lignocaine 160 mg was more unpleasant and produced a change in voice character.

INITIAL INHALATION

At 15 min following the initial nebulisation mean FEV₁ had fallen by 0.04 (95% CI: 0.003–0.08) l (1.5%) from baseline after saline and had increased by 0.42 (95% CI: 0.35–0.5) l (16%) following salbutamol (Fig. 1).

SUBSEQUENT INHALATION

Following inhaled saline

Inhalation of saline and lignocaine 40 and 160 mg caused a transient fall in mean FEV₁ (Fig. 2). The maximum individual fall in FEV₁ was 0.4, 0.5 and 0.87 l (16, 16 and 26% of baseline) and the mean maximum fall in FEV₁ was 0.13, 0.19 and 0.23 l (5, 7 and 9% of baseline) following saline, lignocaine 40 and 160 mg respectively (ANOVA: *P*=0.2). The difference between saline and lignocaine 160 mg was 0.11 (95% CI: -0.03–0.23 l). FEV₁ had returned to baseline by 30 and 45 min after inhalation of saline and lignocaine, respectively. There was no relation between maximum change in FEV₁ following lignocaine and baseline FEV₁ or methacholine PD₂₀.

Bronchial reactivity to methacholine was measured in the 19 subjects on all three occasions. Methacholine PD₂₀ did not differ significantly following inhalation of lignocaine and saline, the differences from saline PD₂₀ being 0.05 (95% CI: -0.44–0.54) and -0.18 (-0.46–0.1) doubling doses following lidocaine 40 and 160 mg, respectively.

Neither dose of inhaled lignocaine had any significant effect on systolic blood pressure or heart rate (both *P*>0.3) although there was a small increase in mean diastolic blood pressure of 3.8 mmHg (95% CI: -0.02–7.46) following lignocaine 160 mg compared with saline, but this was not significant (*P*=0.09).

Following pretreatment with salbutamol

There was no fall in FEV₁ following inhalation of lignocaine 40 or 160 mg after pretreatment with salbutamol (Fig. 1).

TABLE 1. Details of age, sex, spirometry, methacholine PD₂₀ and usual treatment for the 20 patients studied

Patient no.	Age	Sex	FEV ₁ (l)	FEV ₁ (% predicted)	Methacholine PD ₂₀ (μmol)	Treatment
1*	43	M	3.0	78	1.54	Salb, FP 250 μg
2	62	M	2.1	62	0.145	Salb, Sm, BDP 800 μg
3	20	M	3.75	84	5.1	Tb
4	48	F	2.6	100	0.58	Salb, Sm, BDP 500 μg
5	59	F	1.3	57	0.59	Salb, BDP 400 μg
6	46	F	2.35	84	6.12	Salb, BDP 400 μg
7	42	M	2.3	65	1.15	Salb
8	56	F	1.35	63	1.1	Salb, BDP 200 μg
9	44	F	2.6	82	1.3	Salb, BDP 400 μg
10	24	M	4.5	100	2.35	Salb
11	38	F	2.3	80	0.17	Salb
12	38	M	3.3	79	0.64	Salb, BDP 400 μg
13	46	M	2.25	59	1.3	Salb
14	51	F	2.4	94	1.2	Salb, BDP 200 μg
15	46	M	3.6	78	6.7	Salb
16	43	M	2.8	70	1.4	Salb, BDP 400 μg
17	53	M	2.5	72	3.06	Salb, BDP 800 μg
18	33	M	3.45	70	5.2	Salb
19	40	M	2.5	68	0.77	Salb, BDP 400 μg
20	62	F	1.7	85	2.7	Salb, Bud 200 μg
Mean (SD)	44		2.6 (0.8)	76.5 (12.6)	1.4** (2.9)	

BDP=beclomethasone dipropionate; Bud=budesonide; FP=fluticasone propionate (dose as daily dose); Salb=salbutamol as required; Tb=terbutaline as required; Sm=salmeterol.

*Subject withdrawn. **Geometric mean.

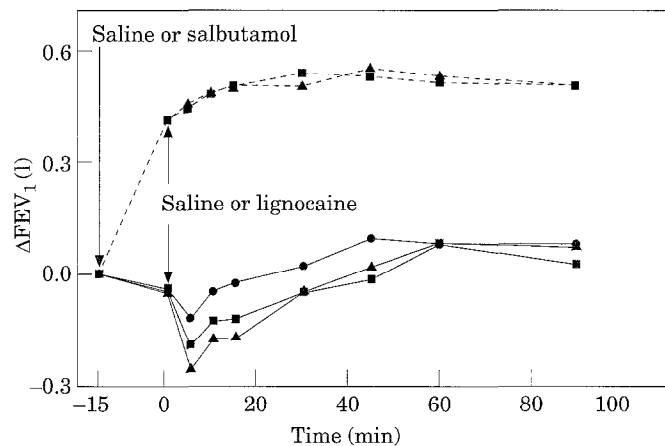


FIG. 1. Change in FEV₁ (l) following initial inhalation of salbutamol (---) and saline (—) and following subsequent inhalation of saline (●), lignocaine 40 mg (■) and lignocaine 160 mg (▲).

Plasma lignocaine levels were 0.35 (SD=0.14) and 0.28 (0.08) μg ml⁻¹ at 30 and 60 min respectively after 160 mg lignocaine. Levels were unaffected by pretreatment with salbutamol.

Discussion

If lignocaine is found to be an effective treatment for asthma it could be a useful alternative to oral prednisolone.

Before embarking on more extensive studies in patients with severe asthma we wished to determine the safety of inhaled lignocaine in patients with less severe asthma because previous studies have reported considerable bronchoconstriction. We found that inhaled lignocaine 40 and 160 mg caused a small mean fall in FEV₁ of 7 and 9%, respectively, but its effect did not differ significantly from the 5% fall that occurred after normal saline. One subject had a large (26% of baseline) fall in FEV₁ following

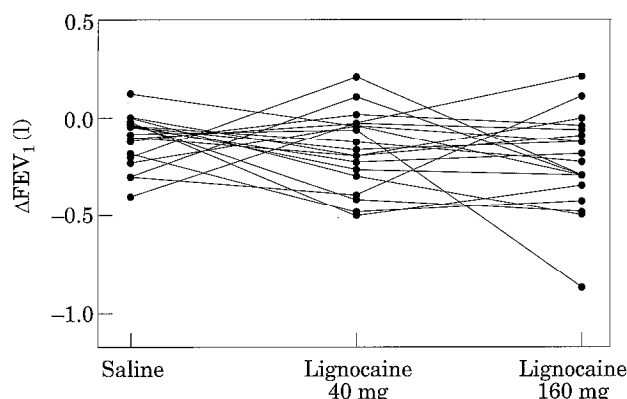


FIG. 2. Maximum change in FEV_1 following saline and lignocaine 40 and 160 mg in individual subjects.

inhalation of lignocaine 160 mg and this was prevented by pretreatment with salbutamol. We found no change in bronchial reactivity to methacholine at 90 min when the local anaesthetic effects of lignocaine had worn off.

Lignocaine is difficult to study because it has a bitter taste which is easily recognized and because oral anaesthesia may affect the ability to carry out spirometry. We attempted to blind the treatment options with a spray of banana-flavoured 4% lignocaine applied to the subject's tongue immediately prior to lignocaine, and saline inhalation. Although it was only effective in masking the lower dose of lignocaine it caused an unpleasant taste and oral anaesthesia on all 5 days so that any effect of a noxious stimulus or oral anaesthesia on the patient's ability to perform spirometry would be similar on all 5 days. Application of the lignocaine spray during expiration should not have affected the airways and up to 10 sprays of 2% lignocaine to the throat had no effect on FEV_1 in asthmatic subjects in a previous study (8).

Four of the five (3–6,9) previous single-dose studies in the literature have reported bronchoconstriction following inhaled lignocaine but interpretation is difficult for the reasons outlined above and because two of the studies were not controlled (5,6). Patients may bronchoconstrict to inhaled normal saline, as in our study, so we cannot be sure that the response in the uncontrolled studies was due to inhaled lignocaine. In the three studies comparing lignocaine and saline, two showed a larger fall in FEV_1 or maximal mid-expiratory flow following lignocaine compared with saline (3,4) whilst the other did not (9). Only one previous study included subjects taking inhaled steroids (6). Taken together these studies suggest that lignocaine can cause bronchoconstriction in some patients with asthma, although the mean fall is less than previously reported. Our study suggests that pretreatment with 2.5 mg salbutamol should protect against any bronchoconstriction but the effects of a smaller dose given by an inhaler are unknown. Since beta-agonists were not withheld during the study by Hunt *et al.* (2) this may explain why only one subject reported chest tightness with no fall in FEV_1 .

Studies carried out within 30 min of inhaled lignocaine or during a lignocaine infusion have shown a small reduction in bronchial responsiveness to methacholine (4), histamine

(10) and acetylcholine (11) but not cold air (12). At these times lignocaine would still have local anaesthetic activity which could inhibit reflex-mediated bronchoconstriction. We performed the methacholine challenge after 90 min so that FEV_1 would have returned to baseline and any effect of local anaesthesia on the ability to carry out spirometry would be reduced. Furthermore if lignocaine has beneficial effects in asthma they will probably need to extend beyond the duration of local anaesthesia.

In agreement with other studies we found no significant change in heart rate or systolic blood pressure following inhalation of lignocaine (9,13). The small increase in diastolic blood pressure of 3.8 mmHg following lignocaine 160 mg was not significant although it is consistent with i.v. studies in humans and dogs (14).

Thus, in our study, patients with mild to moderate asthma did not bronchoconstrict significantly more to lignocaine than to normal saline. When a bronchoconstrictor effect was seen it was inhibited by pretreatment with salbutamol. It is possible that patients with more severe asthma may have more marked bronchoconstriction and we are now studying the safety and efficacy of inhaled lignocaine in oral-steroid-dependent patients.

Acknowledgement

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